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CASE SERIES

Contrast-enhanced Ultrasound of Kidneys in Children with Renal Failure

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Ultrasound (US) has been an important tool for evaluating and imaging renal pathology in children. Development of US contrast agents and dedicated software for the detection of microbubbles has given this radiological investigation a new dimension, especially in children with renal impairment. Application of contrast-enhanced US (CEUS) brings US into the domain historically occupied by computed tomography and magnetic resonance imaging. We retrospectively studied nine children who had undergone CEUS (age range 3—16 years). This pictorial essay draws on our experience and illustrates the safety and accurate depiction of enhancement pattern of focal renal lesions.

Introduction

Conventional ultrasound (US) has been the mainstay of the imaging renal system and abdominal organs in clinical practice, especially in the pediatric age group. With its advantages of being a nonradiating modality and real-time imaging, US has become essential in radiological evaluation in children. The advent of microbubble contrast-enhanced US (CEUS) has added a new dimension to this essential role and has the potential of offering insights to enhancing patterns of organs and masses similar to, if not better than, conventional computed tomography (CT) and magnetic resonance imaging (MRI) [1]. We provide an overview of the use of CEUS for assessment of renal diseases in children in our hospital.

As US contrast agents consist of microbubbles, and thus are blood pool agents, implying that they do not leave the blood vessels and are not subjected to normal renal filtration nor excretion, they essentially behave like vascular tracers.

The risk of water-soluble, contrast-induced nephrotoxicity and nephrogenic systemic fibrosis with gadolinium in patients with renal compromise (estimated glomerular filtration rate $<$ 30mmol/L) has essentially limited the role of contrast-enhanced CT and MRI in such patients. A conventional US kidney is often suboptimal in assessment of

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renal lesion characteristics [2]. Therefore, US contrast agents, with their relative safety and low incidence of side effects, offer a unique perspective to renal imaging. They are not nephrotoxic or cardiotoxic and are excreted in the lungs, and thus, their use does not require renal function tests to be performed prior to administration [1,3]. Riccabano and Darge et al and Riccabano and Avni et al all have found ultrasound contrast agents to be quite safe in use of children [4,5]. A large retrospective analysis showed that SonoVue has a good safety profile in abdominal applications, with an adverse event rate lower than or similar to that reported for radiological and magnetic resonance contrast agents [4,5].

SonoVue (sulfur hexafluoride by Bracco, Milan, Italy) is the only sonographic contrast available in our hospital and was used in these studies. SonoVue is phospholipid-encapsulated sulfur hexafluoride microbubbles with an average bubble diameter of 2.5 μm. Five milliliters of normal saline was added to SonoVue powder to form a suspension, and 1.5 mL of microbubble suspension was quickly injected via a peripheral vein (in which a 20 G intravenous cannula had been earlier inserted), followed by rapid bolus injection of 5 mL normal saline. We typically injected up to two boluses of well-dispersed microbubble suspension at an interval of 10—15 minutes. We selected appropriate positions, depending on different needs to perform coronal, sagittal scans of the kidneys. Gray scale US was conducted to observe tumor size, shape, echo intensity, and demarcation from adjacent tissues while color Doppler was used to examine the blood flow within and outside of the tumors. CEUS was performed by fixing a probe targeted at the mass following selecting a suitable section.

US equipment used in this study was AS500 (Toshiba Medical, Tokyo, Japan) and IU22 (Philips Medical, Amsterdam, The Netherlands), with contrast imaging mode on these machines.

Renal lesions were compared with their corresponding normal renal cortex. Lesions with post SonoVue enhancement higher than, lower than, or equaling that of the cortical echogenicity were defined as hyperenhancing, hypoenhancing, and isoenhancing, respectively. The vascular phases were classified into cortical (from 8—15 seconds to 30—35 seconds after injection), corticomedullary (from 36—41 seconds to 120 seconds), and late phase (> 120 seconds to the disappearance of bubbles) [6—8]. The differences in initial enhancement, the enhancement extent, and pattern were compared between the lesion and the peripheral renal cortex. The enhancement extent was classified into hyperenhancement, isoenhancement, and hypoenhancement compared with the surrounding renal parenchyma. In addition, the time in which the contrast agent entered and exited the mass was also compared with that of the rest of the normal. "Fast in" and "fast out" means that inflow and outflow of the contrast agent into and from the mass is earlier than as compared to the rest of the renal cortex; "identical in" and "identical out" mean that the contrast agent enters and exits the mass and the normal renal cortex at the same time; and "slow in" and "slow out" mean that inflow and outflow of the contrast agent are later in the mass than in the normal cortex. According to CEUS features, comparisons between renal lesions and their surrounding tissues, the dynamic change patterns of lesions in kidney and bladder were divided into six types, that is, fast in and fast out (FIFO), fast in and slow out (FISO), identical in and fast out (IIFO), identical in and identical out (IIIO), fast in and identical out (FIIO), and slow in and slow out (SISO) [9].

We present a group of nine children who had undergone CEUS, age range 3—16 years. Written informed consent was obtained from the parents before the study and the referring clinician was present on site at the time of the study. All these children presented with deranged renal function (estimated glomerular filtration rate < 30 mmol/L) and had undergone other limited cross-sectional imaging examinations which were equivocal for underlying disease. As the use of SonoVue in children is not approved by the Singapore Health Authority, it was only used as the last viable option for these children with renal failure, for whom further contrast imaging with CT or MRI was not possible. The decision to perform CEUS was made as a prelude to possible surgical intervention and/or biopsy. No episode of allergic reaction or post procedure complication was encountered in any of the assessed patients.

Renal cysts

Characterization of complex renal cyst remains a common and sometimes difficult diagnostic dilemma for the referring urologist and radiologist. These are routinely found incidentally on radiological investigations. Whether a cyst enhances or not, is important in differentiating it from being a malignant lesion, as the chance of neoplasia increases to 40—80% when there is enhancement noted [8]. Although contrast CT/MRI is the gold standard, CEUS has given evaluation of complex renal cyst a new dimension. CEUS has the advantage of being able to visualize the thin fine septa better than CT [2,10]. Fig. 1 shows a simple cyst in the kidney, with no nodular enhancement of the cyst wall, and no internal septae or delayed washout. Fig. 2 shows a complex renal cyst, with mild enhancement of the internal septae. However, no nodular enhancement of the septa and no washout within the cyst or septae is seen, rendering it a Bosniack II cyst.

Renal angiomyolipoma

Renal angiomyolipoma shows filling in of the contrast agent starting from the periphery of the echogenic mass and slowly extend to the center of the lesion with iso- or hypoenhancement to the rest of the normal renal cortex. This is most likely due to the presence of malformed blood vessels with tortuous course and disorganization. These anatomical features associated with renal angiomyolipoma result in SISO of the contrast agent, thus the start of the inflow and outflow of the contrast agent is both later in the mass than in the renal cortex. Fig. 3 shows a typical renal angiomyolipoma, where the lesion is seen to be less enhancing than the adjacent normal renal parenchyma at all phases, that is, arterial, portal-venous, and delayed phases.

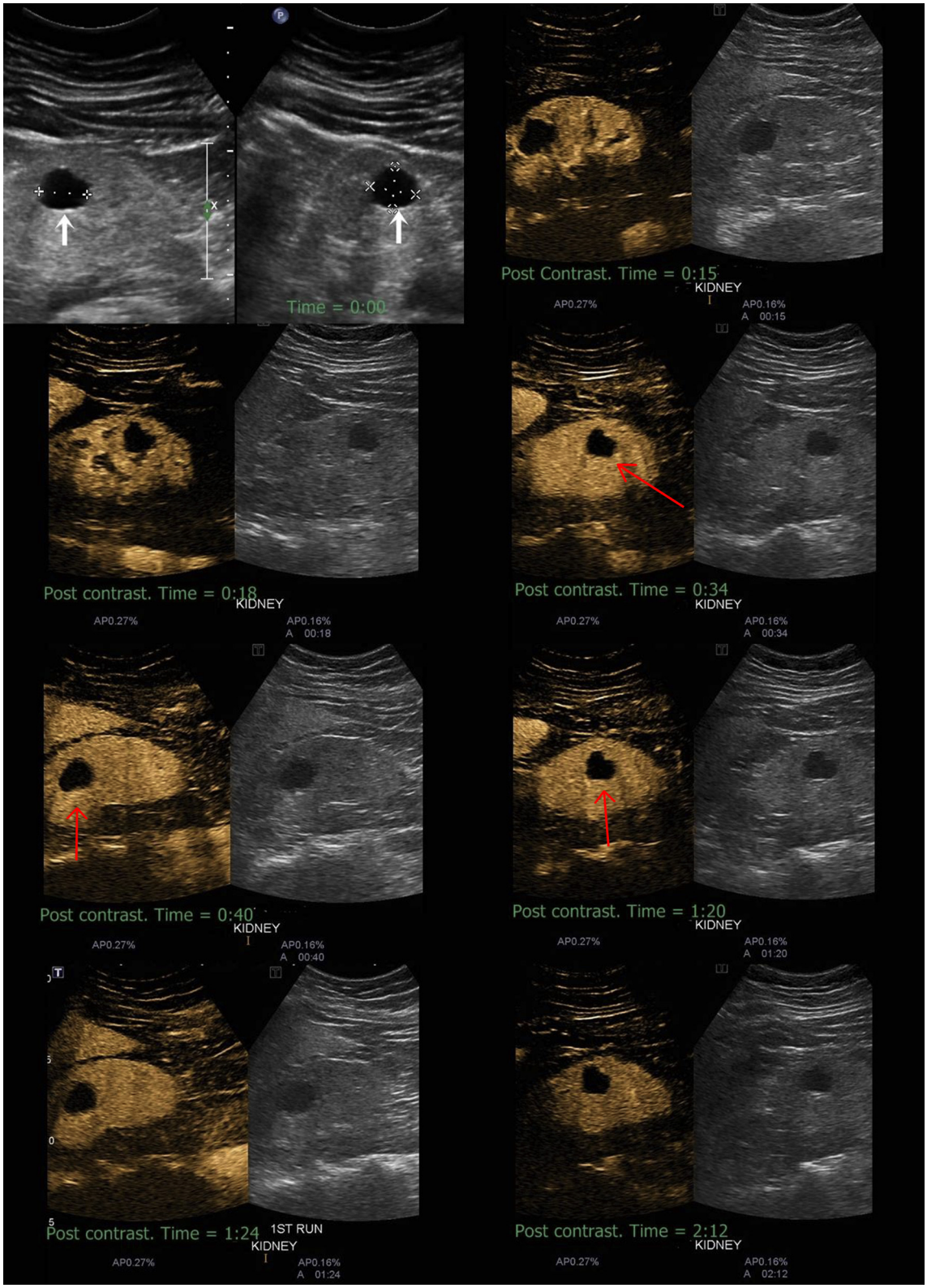

Fig. 1 Simple renal cyst. Contrast-enhanced ultrasound shows cyst with anechoic cyst without septa, calcification, or solid components. No enhancement is noted after intravenous contrast agent injection. It is characteristic for a simple Bosniak Type 1 cyst and does not entail further investigation.

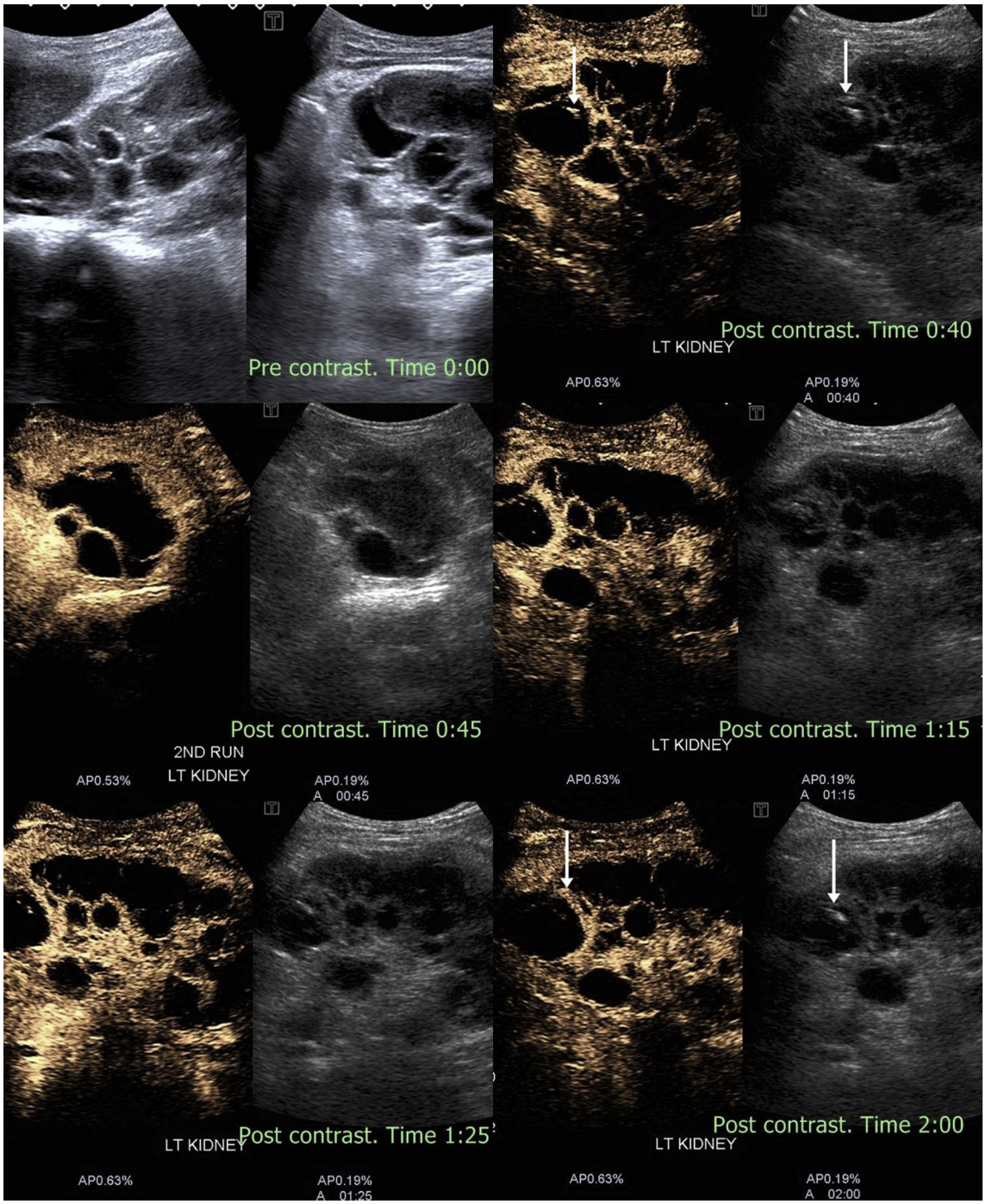

Fig. 2 Complex renal cyst. Noncontrast ultrasound shows a large renal cyst with solid echogenic component within the cyst. Post-contrast images show no intracystic enhancement and the apparent echogenic solid lesion (white arrow) shows no arterial enhancement or washout. It was proven on follow-up imaging to be a complicated cyst with some internal hemorrhage.

Renal perfusion

CEUS agents do not leave the blood vessels and are not subjected to renal filtration and thus behave like vascular tracers. Using CEUS to identify the vessels rather than Doppler to track the course of the renal artery has been shown to be accurate and shortens examination time in large patients, and of course can be used in patients with renal impairment [11].

CEUS is a good modality to assess the perfusion pattern of a kidney. After contrast injection, there is immediate and prompt enhancement of the kidney, usually seen within 10 seconds post-injection. The main renal artery, its bifurcation, the arcuate and segmental arteries are

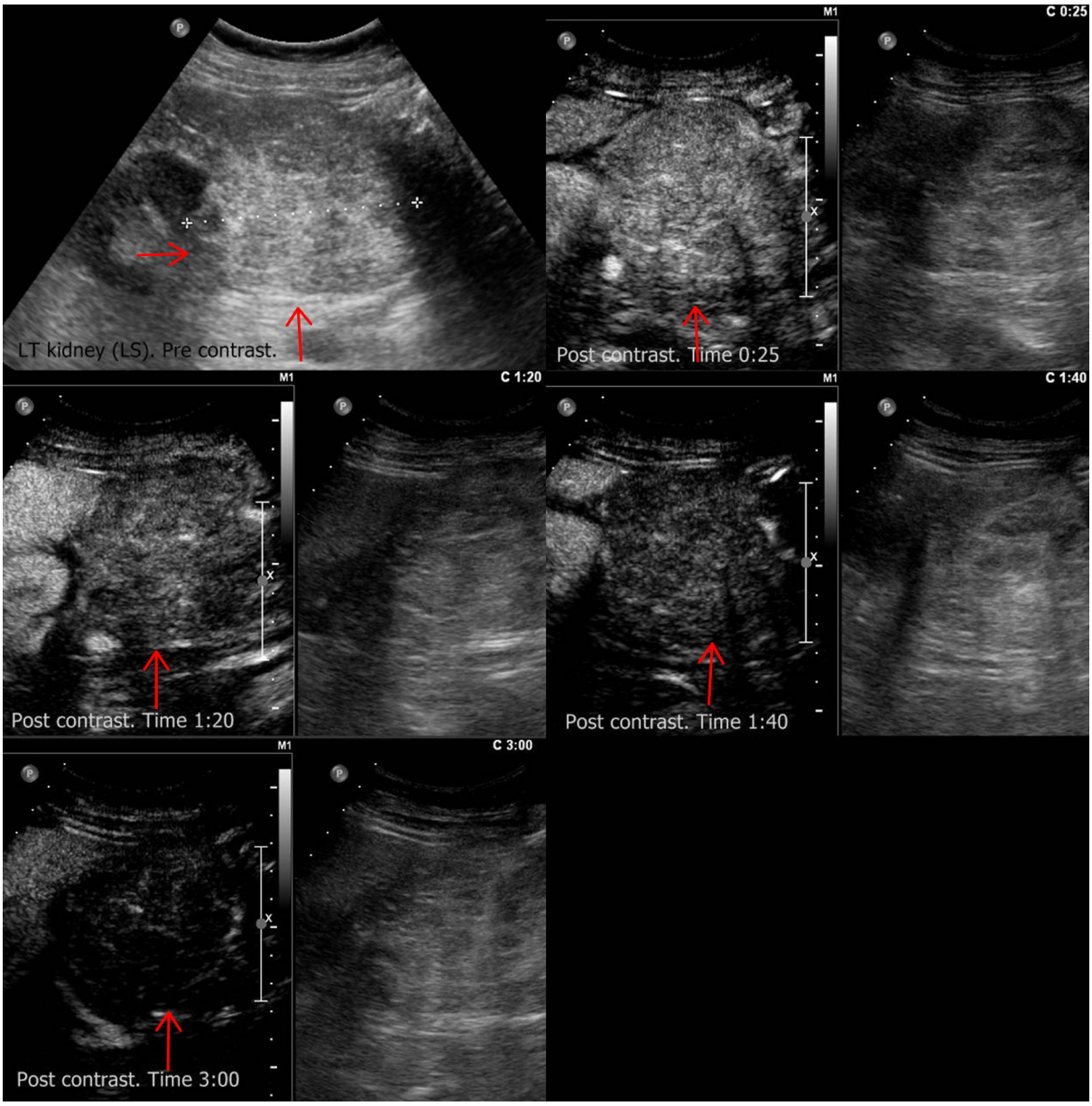

Fig. 3 Renal angiomyolipoma in an 8-year-old boy, with incidental note of a left kidney mass on bedside ultrasound. Noncontrast images show a large echogenic exophytic mass, which shows postcontrast enhancement, which is less enhanced than the normal renal parenchyma on all phases. No significant washout is seen within the lesion.

promptly enhanced and perfusion can be seen up to the periphery of the cortex. We present a case in which a 14-year-old child with known bilateral renal artery stenosis suddenly became anuria after an attempt of bilateral renal artery angioplasties (Fig. 4). Noncontrast magnetic resonance angiography of the abdominal vessels could not demonstrate the renal arteries (Fig. 5). Hence, a clinical concern of bilateral renal artery embolization or dissection was raised, which is a known post-angioplasty complication. The possibility of auto-transplantation was being considered in view of deteriorating renal function. A decision was made to perform bedside CEUS to prove or disprove if there was viable perfusion within the kidneys. As our images show (Fig. 6), there was prompt enhancement of the kidneys, with homogeneous cortical enhancement. No perfusion defects were visualized and the underlying condition was deemed secondary to spasm of the renal arteries. The renal function recovered over time with conservative management.

Nephronia

A 16-year-old boy noted positive findings on urine microscopy and being treated for urinary tract infection. Post-contrast US of the echogenic heterogeneous mass in the kidney showed enhancement similar to the rest of the renal parenchyma, with areas of nonenhancement in the center of the lesion. No washout was noted within this lesion. These features are similar to CT imaging features of lobar nephronia.

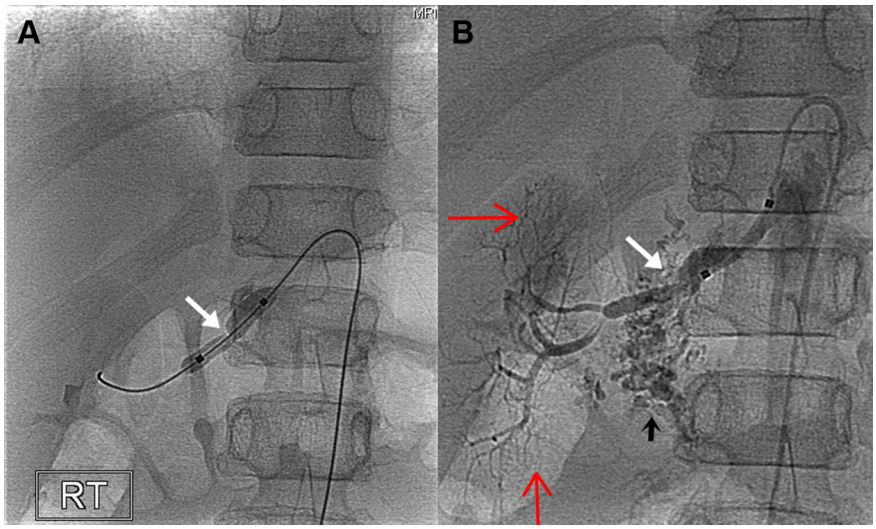

Fig. 4 Angiographic perfusion. (A) Angiography of the renal artery shows narrowed main renal artery. (B) Multiple collateral around the main renal artery and distal intrarenal vessels are visualized (red arrows).

Focal pyelonephritis and renal abscess

In an appropriate clinical context, CEUS can be used as an accurate tool in assessment of renal infection and inflammatory renal masses. Focal nephronia can often present as a well-defined mass and causes much confusion and worry to pediatricians and parents; and CEUS has shown to improve sensitivity. Regional differences in parenchymal enhancement are easier to detect than those affecting the entire kidney since the normal parenchyma serves as an internal reference.

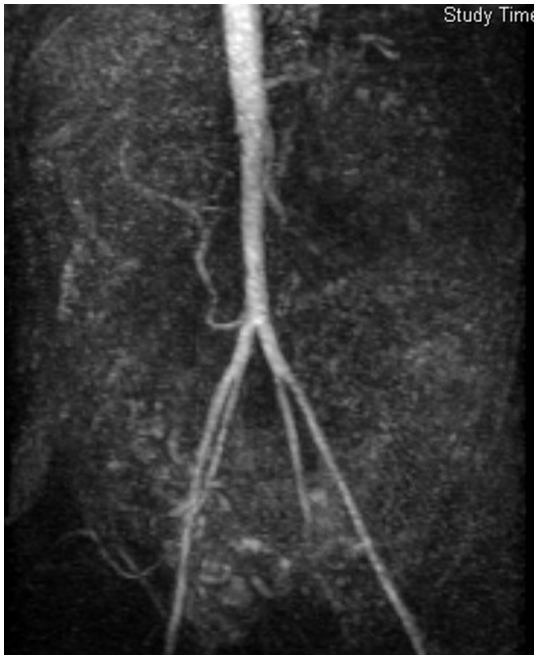

Fig. 5 Magnetic resonance angiography (MRA-TOF) of the abdominal aorta. This image shows non-visualization of the renal arteries and the renal parenchyma, raising suspicion for an embolic or ischemic insult to both kidneys, post-angioplasty attempt.

The characteristics on MRI and CT can be nonspecific and there can be persistent clinical dilemma. We present such a case in which an 8-year-old boy presented with chills and fever, which was of short duration and subsequently subsided. On initial US, a well-defined heterogeneously echogenic mass was noted in the right kidney. On follow-up, contrast-enhanced nondynamic MRI of the kidneys revealed a persistent rounded mass, but the imaging characteristics were nonspecific and the possibility of a malignant lesion was considered. Subsequently, the child developed some renal impairment and follow-up contrast-enhanced axial imaging was deferred. A clinical decision was made to perform an open biopsy and possibly tumor resection. Bedside CEUS was arranged and written consent was obtained from the parents. CEUS showed a heterogeneously enhancing lesion, with nonenhancing areas in the center of the lesion. No significant washout was seen and the possibility of focal nephronia and abscess was considered (Fig. 7). Follow-up US was performed 2 weeks later, after a course of antibiotics, which showed resolution of the focal lesion.

Children with pyelonephritis can develop renal abscess as a complication. As conventional US is poor at depicting, or confidently identifying these early renal abscesses, especially when they present at solid lesions in the kidney. CEUS shows a heterogeneous lesion with central nonenhancing areas with a thick enhancing rim and a small, low-attenuation perinephric fluid collection. There is peripheral enhancement of the lesion with contrast, with no central enhancement and no washout on delayed images (Fig. 8).

Pseudotumors

Certain renal anatomic variants, such as persistence of fetal lobulation, hypertrophied column of Bertin, and dromedary hump, may present as or have appearances

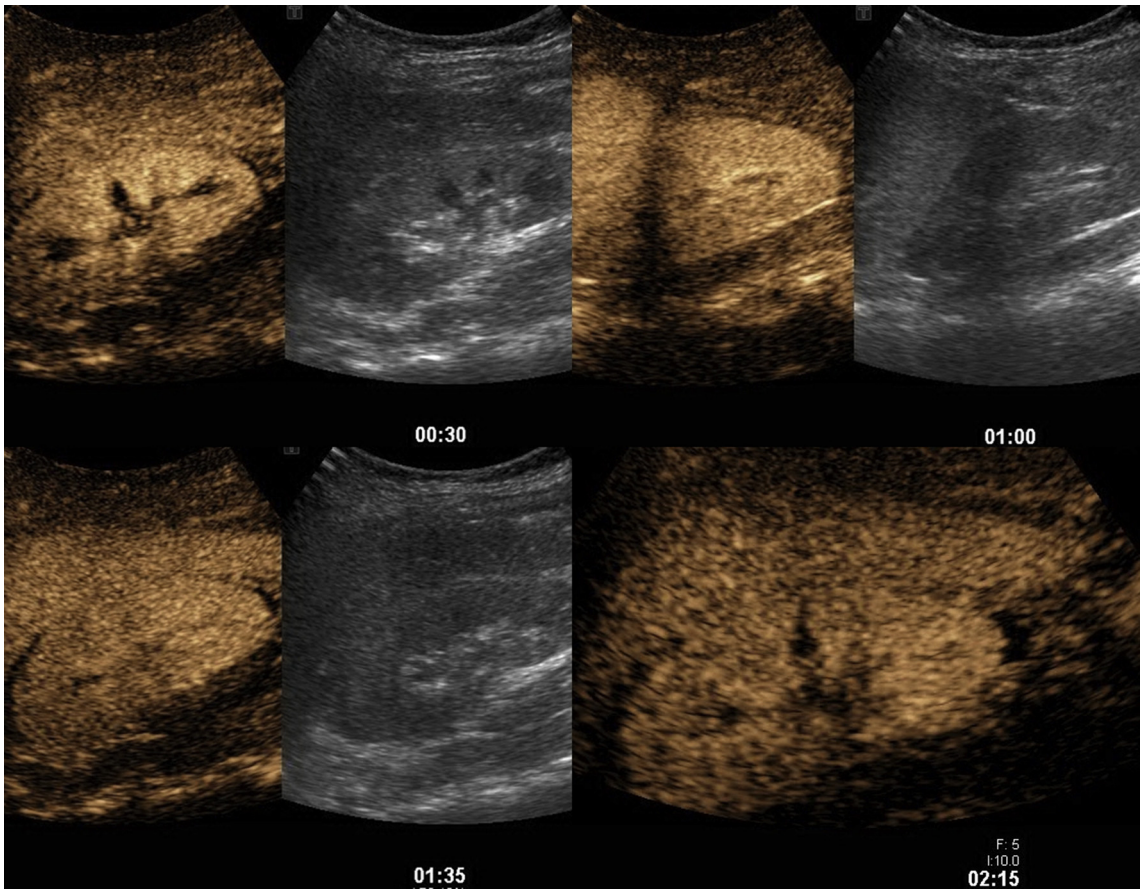

Fig. 6 Renal perfusion. Post-contrast-enhanced ultrasound shows prompt homogeneous uniform enhancement of both kidneys, with no perfusion defects or areas of ischemia/necrosis. These images excluded the possibility of a thromboembolic episode within the kidney and shows that the renal arteries were patent.

similar to a solid mass lesion on imaging [9]. There is a constant dilemma of overcalling or undercalling these lesions and conventional US may not suffice to differentiate or further characterize these lesions. Frequently, these patients do get subjected to further cross-sectional imaging such as CT and MRI and published evidence to the role of CEUS is limited. However, we feel that CEUS can be used to identify these renal pseudotumors confidently, thus avoiding the more expensive or invasive CT or MRI. Characteristically, all pseudotumors on CEUS would enhance homogeneously at the same time as the rest of the normal renal parenchyma and the rate of contrast washout would also be the same, just like normal renal parenchyma. Fig. 9 depicts an apparent mass on conventional US, which on post-CEUS shows homogeneous and uniform enhancement, which is seen to enhance and washout at the same time as the rest of the normal renal parenchyma.

Malignant masses

Renal cell carcinoma is characterized by numerous thin-walled blood vessels with rich blood flow physiologically and intra-tumor necrosis, hemorrhage, and calcification which are common [12]. Renal cell carcinoma enhances quickly and intensely after contrast administration due to the abundant blood flow (Fig. 10). Afterwards, the microbubbles are washed out rapidly in comparison to the adjacent normal renal parenchyma [8]. It is deemed that almost all malignant renal masses show such similar imaging characteristics on CEUS, with immediate contrast enhancement and delayed washout (appearing less enhancing than the adjacent renal parenchyma on delayed images).

Discussion

Trillaud and colleagues have studied CEUS in comparison with traditional CT and MRI to classify liver lesions and found that the specificity and sensitivity to confirmative histology to be satisfactory [13]. At present, however, few studies are available on the use of CEUS for renal lesions, especially in children.

CEUS is useful in children, as this reduces the radiation burden of CT, and intravenous contrast ultrasound may be useful in similar indications in adults (such as differential of focal lesions in parenchymal organs, organ perfusion). CEUS has proven to be an excellent tool in assessment of renal perfusion, renal infection (abscess), solid and cystic renal masses (cysts, angiomyolipomas, and neoplastic lesions), and pseudomasses.

Conventionally, contrast CT is the gold standard for assessing renal masses. However, contrast CT has some

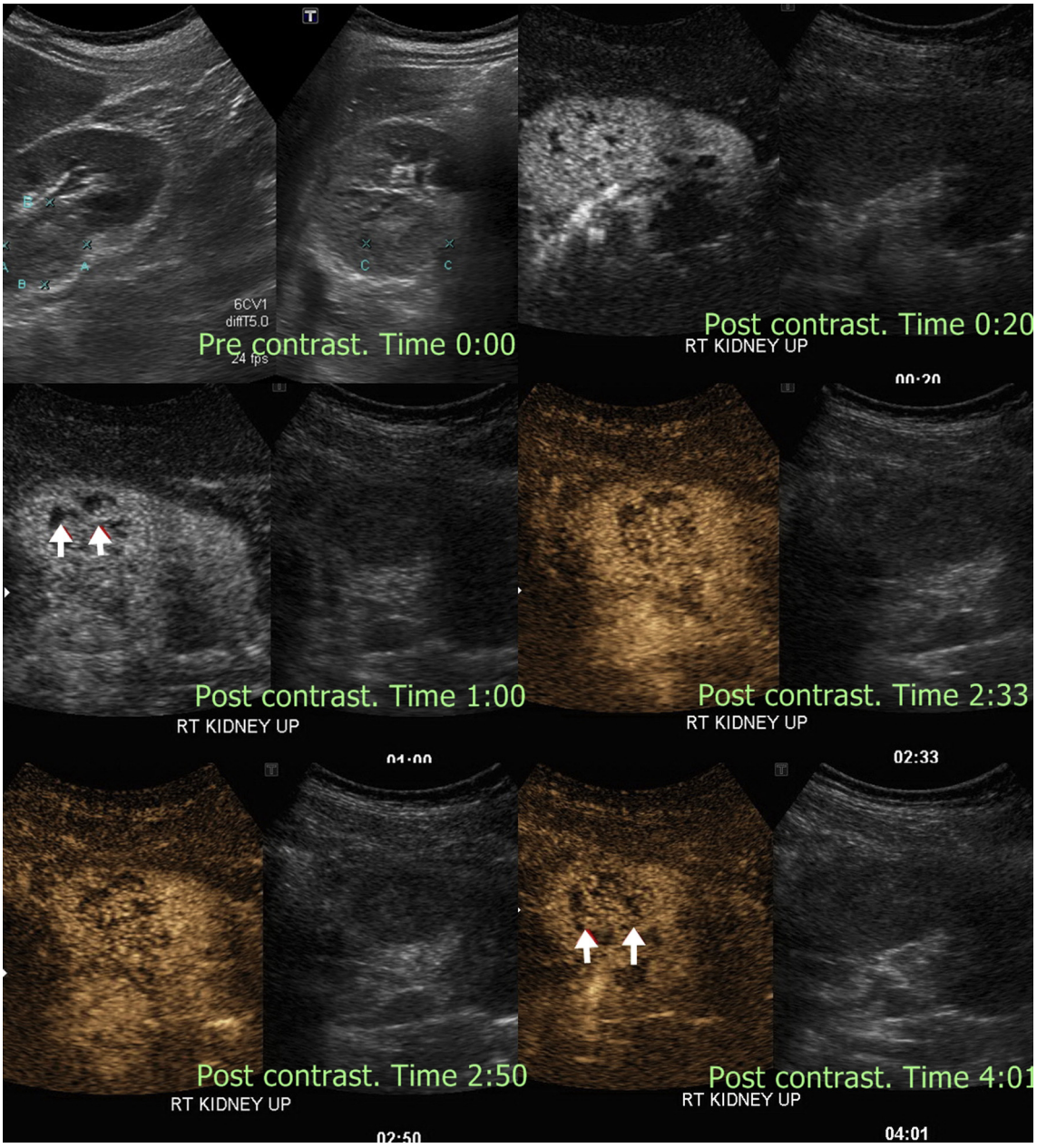

Fig. 7 Nephronia. A 16-year-old boy with positive findings on urine microscopy and being treated for urinary tract infection. Post-contrast-enhanced ultrasound of the echogenic heterogeneous mass in the kidney shows enhancement similar to the rest of the renal parenchyma, with areas of nonenhancement in the center of the lesion (arrow). No washout was noted within this lesion. These features are similar to computed tomography imaging features of lobar nephronia.

limitations: it cannot be performed in patients with impaired renal function; and it cannot be used in patients with previous history of contrast reaction. If a patient is to be followed up for an indeterminate mass, multiple CT will be required, which will expose patients to high quantities of radiation and the associated risks, which is especially important in the pediatric age group. Although Doppler is a useful tool to assess vascularity in a renal lesion on conventional US, certain subtle features, such as thin fine septa or small nodules, may be hard to detect with color flow Doppler. CEUS has the advantage of being able to visualize the thin fine septa seen on US and relies on visualizing the enhancement of vessels with contrast using harmonic imaging as compared to color flow Doppler. There is an added advantage of its portability, where it can be performed even in sick children who are unable to be transported to the imaging department. There are literature reports to suggest that CEUS performed better than CT in the depiction of tumor vascularity in the septa of cystic renal masses and hence contrast enhancement [13,14]. McCarville et al [15] have shown that CRUS of evaluation of abdominal tumor is feasible.

The main benefits of CEUS over other investigation modalities in assessing renal pathology in children is that US

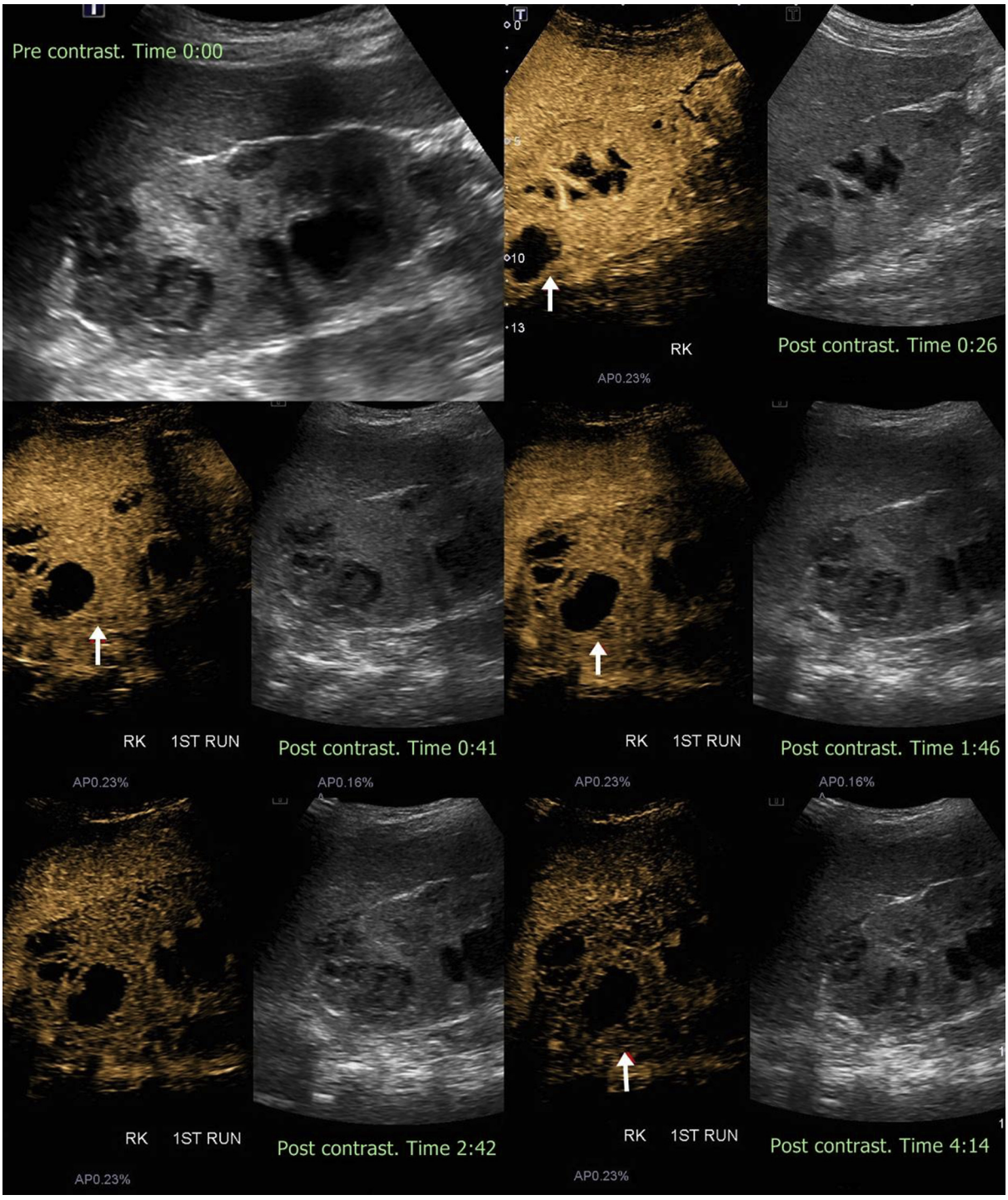

Fig. 8 Renal abscess. A 10-year-old boy being treated for recurrent urinary tract infection. Bedside ultrasound is performed to look for secondary renal findings, due to persistent high fever (38°C), and elevated C-reactive protein markers. Noncontrast images show a heterogeneous hypoechoic lesion. After contrast-enhanced ultrasound, there is a prompt enhancement of the periphery of the lesion (arrow), with no central enhancement and no delayed washout. The enhancement timing is similar to the rest of the renal parenchyma.

contrast agents are not nephrotoxic and can be used safely in patients with impaired renal function [8]. Such an advantage, coupled with lack of ionizing radiation [16] adds value to assessment of renal diseases. The real contraindication for the use of CEUS would be a history of acute cardiovascular disease, right to left shunts, ongoing myocardial infarction, severe rhythm disorders, and severe respiratory failure including respiratory distress syndrome.

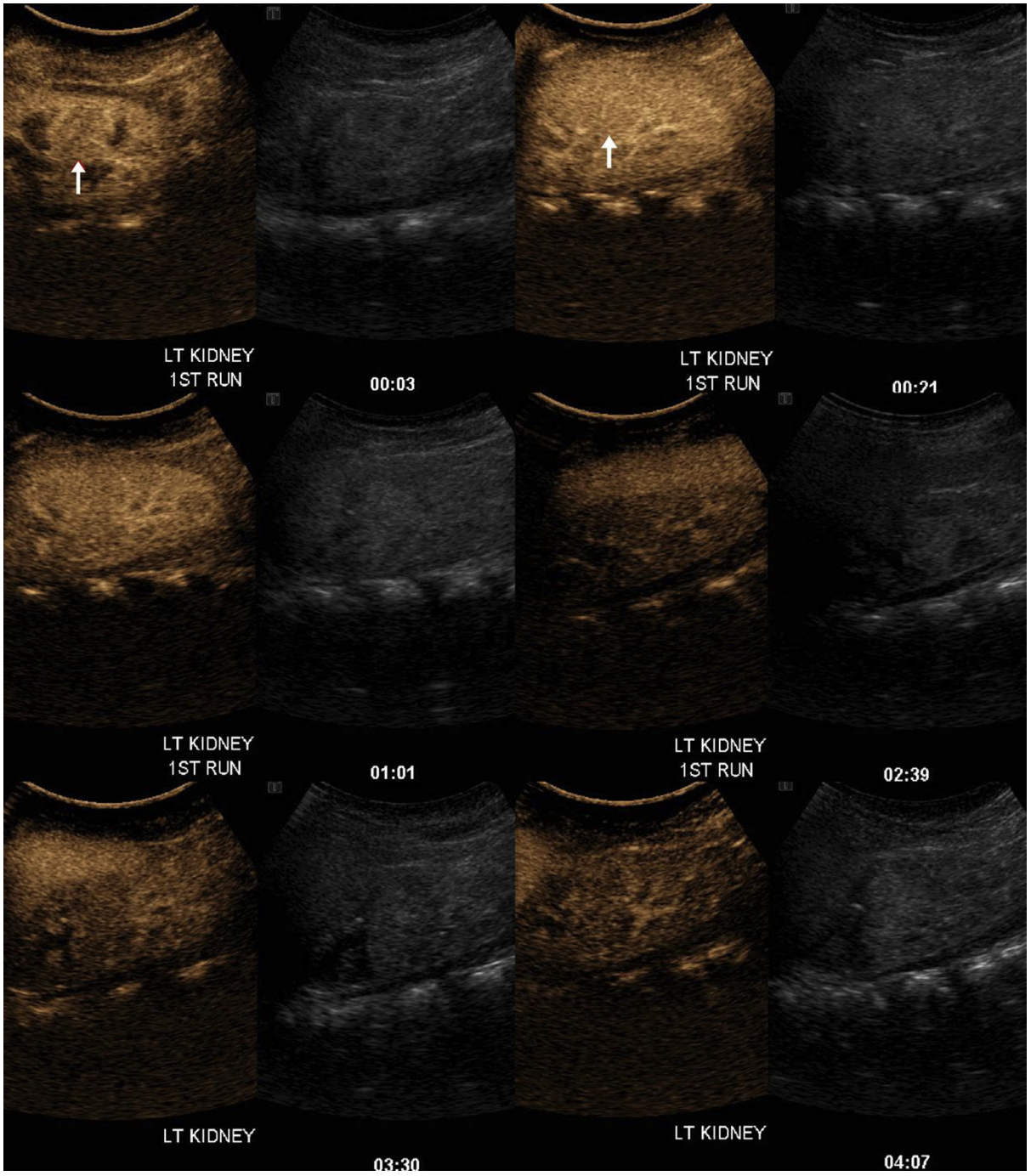

Fig. 9 Pseudotumor. A 15-year-old girl, with incidental findings of a nonspecific mass on bedside US. Noncontrast-enhanced US shows an area of apparent altered echogenicity (arrow) in the interpolar region of the kidney, which is suspicious for a possible mass lesion. Post-contrast-enhanced US shows prompt and homogeneous enhancement in this area, with similar enhancement to the rest of the kidney, with no abnormal enhancement or washout, thus proving this to be normal renal tissue, likely to be prominent Column of Bertin. US = ultrasound.

Care should be taken in patients with chronic obstructive pulmonary disease and pulmonary hypertension, and these patients should be monitored.

The use of CEUS as an imaging modality does have some limitations: a relatively short diagnostic window needing two contrast injections for the same kidney or one injection for each kidney. Simultaneous assessment of more than one focal lesion may be difficult and may require multiple injections in the same sitting. In general, US is relatively harder to interpret in obese patients and bowel gas can interfere with images. Patient compliance is required as the mass may not be visible in one particular position. Contrast agents for CEUS are not yet approved for general pediatric use. Due to the lack of official approval from the

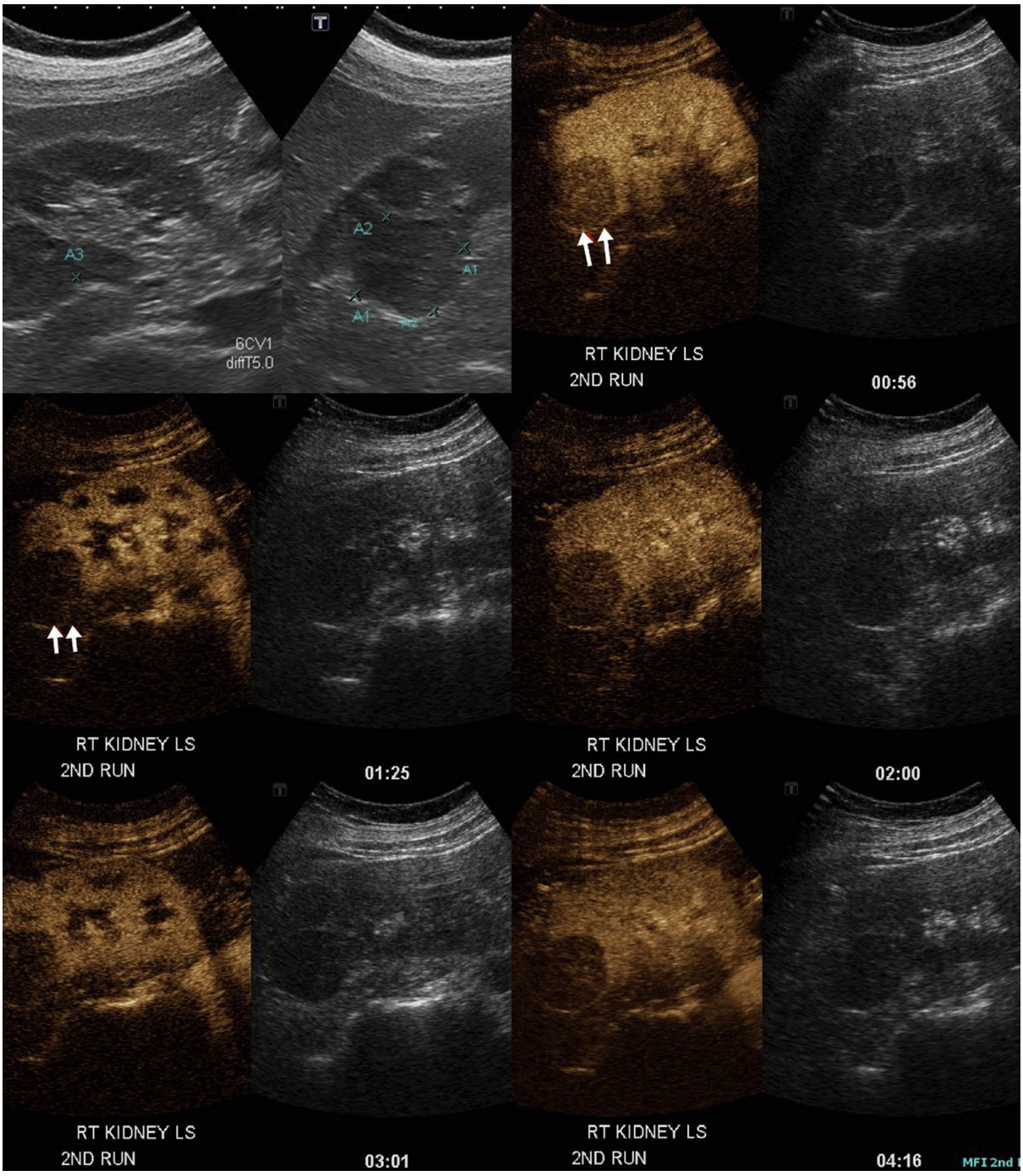

Fig. 10 Renal cell carcinoma. A 13-year-old boy presented with hematuria for investigation. Following contrast administration, the lesion shows homogeneous central enhancement within the lesion (double arrows), which appears less enhanced as compared to the rest of the renal parenchyma. However, it shows washout in the delayed images (double arrows) and appears suspicious for a malignant lesion. It was histologically proven to be a renal cell carcinoma.

Health Science Authority of Singapore for the use of SonoVue, in our hospital, we have limited the use of CEUS as a last resort only in those children who have compromised renal function and other imaging modalities are equivocal in arriving to a diagnosis.

CEUS is an accurate, relatively cheap, and non-radiation modality, with accurate depiction of enhancement patterns of focal renal lesions. It is safe to be used in children with renal insufficiency and renal failure and appears to have minimal incidence of contrast allergy. None of the patients in our cohort had an allergic response to SonoVue. Its accuracy is at least similar, if not more than CT or MRI in the assessment of focal renal lesions and can be used as a modality of choice for solitary focal renal lesions in the presence or absence of renal insufficiency [17,18]. Its role in the pediatric age group has been less defined and further

studies should be performed to validate its use a safe and viable alternative to CT and MRI imaging for renal diseases.

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